Breaking Rings and Building Bonds: Decoding Monobactam–PBP1b Interactions

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BACKGROUND

Antimicrobial resistance:

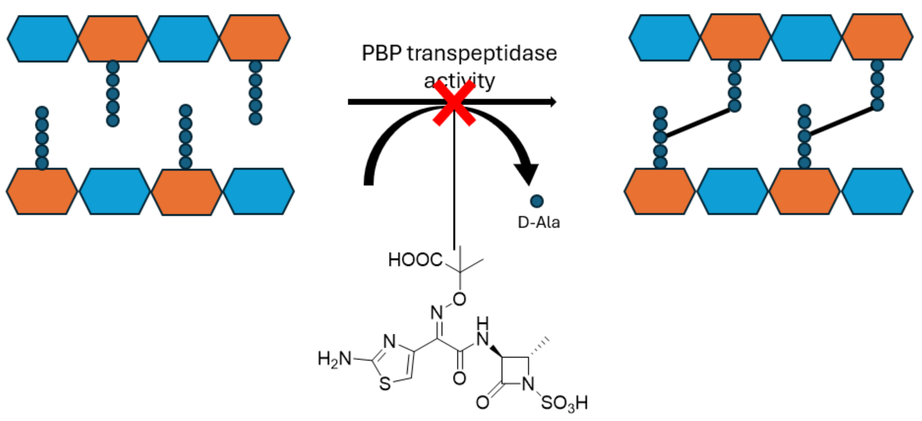
- causes 4.7 million deaths annually

Penicillin-binding proteins:

- form peptidoglycan crosslinks via active site serine
- targeted by β-lactam antibiotics

Aztreonam:

- only monobactam (monocyclic β-lactam) on the market
- high intrinsic stability against common β-lactamases
- resistant to metallo-β-lactamases [2]



METHODS

Computer-aided drug design

- *In silico* library formation
- Pharmacophore model
- 2D similarity
- Virtual screening

Chemical synthesis and purification

- Starting of commercially available β-lactam core
- Forming amides
- Attaching various sidechains

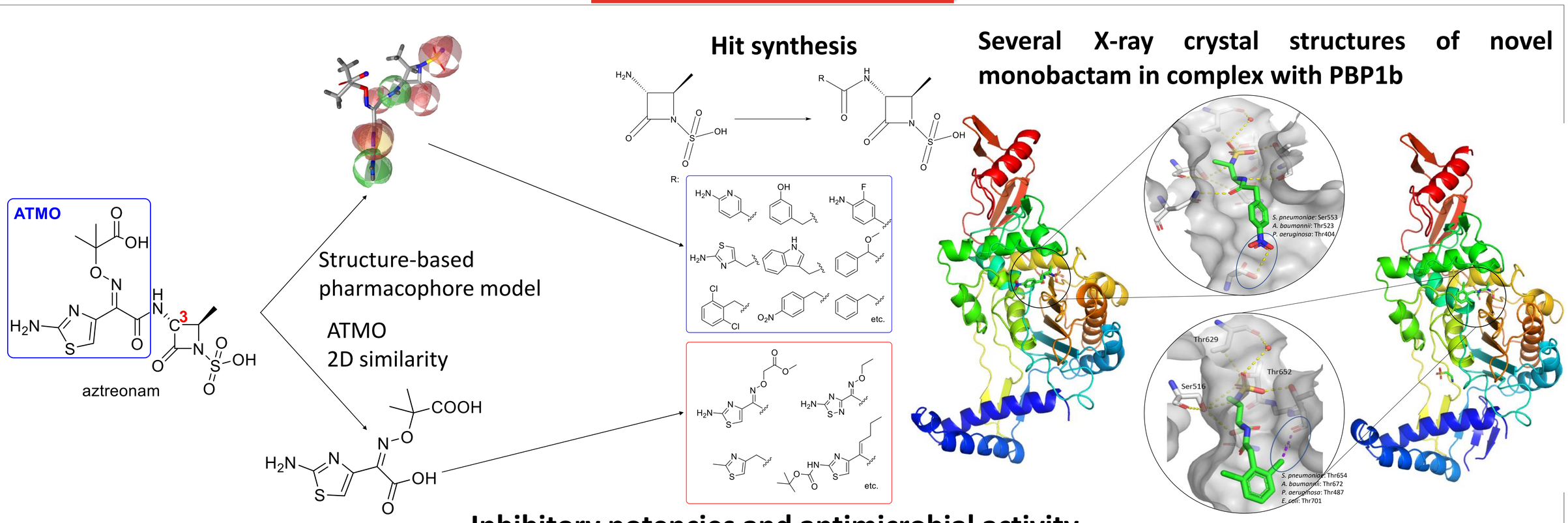
Biological evaluation

- Inhibition of a model PBP – PBP1b from *S. pneumoniae*
- MIC determination

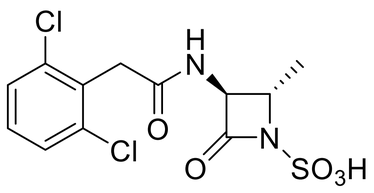
Structure determination

- X-ray crystallography (*S. pneumoniae* PBP1b – monobactams complexes)

RESULTS



Inhibitory potencies and antimicrobial activity



Enzyme inhibition

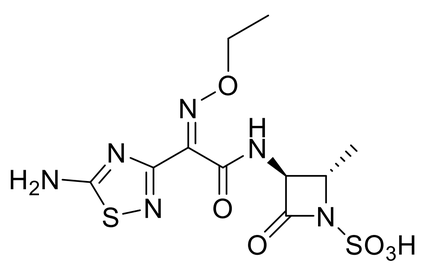
IC_{50} = **0.042 µM**

Antimicrobial activity (MIC)

S. aureus = **64 µg/mL**

E. coli > **128 µg/mL**

A. baumannii > **128 µg/mL**



Enzyme inhibition

IC_{50} = **3.5 µM**

Antimicrobial activity (MIC)

S. aureus > **128 µg/mL**

E. coli = **4 µg/mL**

A. baumannii = **16 µg/mL**

CONCLUSIONS

- Monobactams with **nanomolar enzyme inhibition** of model PBP
- **Several crystal structures** of novel monobactam inhibitors in complex with PBP1b, showing new interactions for simpler monobactams
- **Excellent basis** for future structure-based design in the space of monocyclic β-lactam inhibitors

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References:

[1] Murray CJL, Ikuta KS, Sharara F, Swetschinski L, Robles Aguilar G, Gray A, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. The Lancet. 2022 Feb 12;399(10325):629–55.

[2] Bush K, Bradford PA. β-Lactams and β-Lactamase Inhibitors: An Overview. Cold Spring Harb Perspect Med. 2016 Jan 8;6(8):a025247.

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